201-14230

DBOWER@rtvanderbilt.com on 01/02/2003 02:53:21 PM

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cc: hvanderbilt@rtvanderbilt.com, RKPRICE@rtvanderbilt.com, JKELSE@rtvanderbilt.com, Jim_Keith@americanchemistry.com

Subject: HPV submission, 61617-00-3

Dear Sir or Madam:

The R. T. Vanderbilt Company, Inc. is pleased to provide the attached robust summary and test plan for the HPV Challenge Program, AR-201. The sponsored chemical is 2H-Benzimidazole-2-thione, 1,3-dihydro-4(or 5)-methyl, zinc salt (2:1), CAS registry number 61617-00-3. The robust summary is in IUCLID format; the summary and the test plan are Acrobat .pdf files. Our HPV registration number is .

If you have any questions or need more information, please let me know.

David Bower

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Testing Rationale
Zinc Mercaptotoluimidazole

CAS Registry Number 61617-00-3

The R. T. Vanderbilt Company, Inc.
P. O. Box 5150
Norwalk, CT 06856-5150 USA

Summary

The R. T. Vanderbilt Company, Inc. is pleased to submit this test plan for zinc mercaptotoluimidazole (Vanox® ZMTI) for review and public comment under the Environmental Protection Agency's High Production Volume (HPV) Challenge Program.

Zinc mercaptotoluimidazole (ZMTI) is used as an antioxidant synergist in natural and synthetic rubber; it improves the performance of the primary antioxidant (such as a hindered phenol), allowing less to be used while maintaining effectiveness reducing the amount of primary antioxidant required to be effective. This use requires negligible water solubility, high organic/oil solubility and low vapor pressure. Existing data and use experience suggest little concern for mammalian toxicity, but structural similarity to other chemicals used in the rubber industry warrants additional testing. Therefore, we propose the following studies to meet the requirements of the EPA High Production Volume Chemical Testing Program:

subchronic toxicity to rats with reproductive and developmental assessments
aquatic toxicity (algal growth inhibition, acute toxicity to aquatic invertebrates and acute toxicity to aquatic vertebrates)
ready biodegradability

Aquatic Toxicology. There are no data on the toxicity of ZMTI to aquatic organisms, and no biodegradability or bioaccumulation studies have been performed on ZMTI. Therefore, we propose an algal growth inhibition study and acute toxicity studies on aquatic invertebrates (*Daphnia magna*) and fish (rainbow trout, Oncorhynchus mykiss). We also propose a ready biodegradability study (OECD 301B).

Acute Toxicity: The acute oral LD_{50} for ZMTI is 800 mg/kg. There are dermal and ocular irritation studies; ZMTI is not a skin irritant but is a slight eye irritant. The acute dermal LD_{50} is greater than 2,000 mg/kg and the acute inhalation LC_{50} is greater than 2.03 mg/l. ZMTI is a dermal sensitizer when tested by the Magnusson-Kligman method. We believe that the acute toxicity data for this material are acceptable and we propose no additional studies in this area.

Mutagenicity: We have conducted a bacterial reverse mutation assay (Ames test) as an initial screen. The results of this assay are negative (i.e., mutation frequency did not increase). The molecular structure does not suggest that it would be mutagenic in other assay systems; this is further supported by the fact that the molecule is used as an antioxidant synergist. Therefore, we do not believe that additional mutagenicity studies are warranted at this time.

Repeated Dose Toxicity: There are no subchronic toxicity, developmental toxicity or reproductive toxicity data on ZMTI. We propose a combined 28-day subchronic toxicity study with reproductive and developmental toxicity screens (OECD 422) to address this.

Reproductive and Developmental Toxicity: There are no developmental or reproductive toxicity data on ZMTI. We propose a combined 28-day subchronic toxicity study with reproductive and developmental toxicity screens (OECD 422) to address this.

Conclusion: The physical properties of zinc mercaptotoluimidazole have been adequately studied; however, additional data are required to meet the requirements of the EPA High Production Volume Challenge Program. Every effort has been made to select studies that will provide the most (and the most reliable) information using the fewest animals possible.

Background Information: Manufacturing and Commercial Applications

Manufacturing

Zinc mercaptotoluimidazole has been manufactured for over 30 years. It is manufactured by batch rather than continuous process. ZMTI is manufactured by converting 2-mercaptotoluimidazole to the insoluble zinc salt by reaction with zinc oxide.

Commercial Applications

The largest commercial use of ZMTI is as a an antioxidant synergist for natural and synthetic rubber. It is typically used at 0.5 to 1 part per every 100 parts of rubber (phr).

Shipping/Distribution

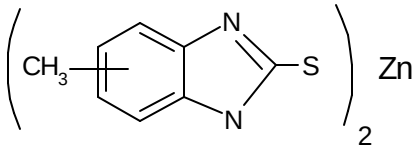
ZMTI is shipped extensively throughout the world from manufacturing plants located in North America and western Europe.

Worker/Consumer Exposure

To the best of our knowledge, all ZMTI is used by the rubber industry, mostly by large industrial users as a component of their rubber compounds. The rubber and plastics additives industry has a long safety record and only sophisticated industrial users handle this material. It is available as a powder and as an aqueous dispersion; the powder is treated to minimize dust generation. Most large industrial users have mechanized materials handling systems, so employee exposure is minimal. The greatest potential for skin and inhalation exposure is at the packing station at the manufacturing site and, to a lesser extent, during weighing activities at the customer site. Nuisance dust is the primary source of worker exposure.

Consumer exposure is minimal. Small amounts are used in rubber processing, and the material becomes bound in the rubber matrix during vulcanization. The most likely route of consumer exposure is skin contact from rubber or latex articles. Skin irritation is unlikely but allergic skin reactions may occur.

STRUCTURE



ZMTI is regulated for use in food-contact applications by the Food and Drug Administration:

> FCN 000201: 2H-benzimidazole-2-thione, 1,3-dihydro-, 4(or 5)-methyl-, zinc salt (2:1) containing up to 4 percent by weight petroleum process oil: As an antioxidant synergist in natural or synthetic rubber gloves intended for repeat use in the meat packing industry. To

be used in equal amounts with the primary currently regulated antioxidant, at no greater than 1 percent by weight of the rubber gloves.

ZINC MERCAPTOTOLUIMIDAZOLE

Test Plan

CAS No. 61617-00-3

R. T. Vanderbilt Company, Inc.
December, 2002

Physical-Chemical

Melting Point	Boiling Point	Vapor Pressure	Partition Coefficient	Water Solubility
A	Calc	Calc	Calc	A

Environmental Fate

Photodegradation	Stability in Water	Transport/ Distribution	Biodegradation
Calc	Calc	Calc	A

Ecotoxicity

Acute Toxicity to Fish	Acute Toxicity to Aquatic Plants (e.g., Algae)	Acute Toxicity to Aquatic Invertebrates (e.g., Daphnia)
Test	Test	Test

Mammalian Toxicity

Acute Toxicity	Bacterial Genetic Toxicity *In Vitro*	Mammalian Genetic Toxicity *In Vivo*	Repeat Dose Toxicity	Reproductive Toxicity	Developmental Toxicity
A	A	NR (1)	Test	Test	Test

Legend

Symbol	Description
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties
SAR	Structure-Activity Relationship

(1) Mammalian genetic toxicity testing is generally not required if the results of *in vitro* mutagenicity tests are negative.

2H-benzimidazole-2-thione, 1,3-dihydro-4(or 5)-methyl-, zinc salt

CAS# 61617-00-3

201-14230B

Molecular Formula: $C_{16}H_{16}N_4S_2Zn$
Molecular Weight: **393.85**

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1.1 GENERAL SUBSTANCE INFORMATION

A. Type of Substance: Organic
B. Physical State: Off-white to tan solid
C. Purity: 95-97%

1.2 SYNONYMS

Zinc mercaptotoluimidazole
Vanox® ZMTI
Vulkanox® ZMB2/C5

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

Value:	300° C minimum
Decomposition:	No
Sublimation:	No
Method:	Determination of melting point using Fisher-Johns melting point apparatus
GLP:	No
Remarks:	None
Reference:	R. T. Vanderbilt Standard Method of Analysis (T-3B)
Reliability:	(1) Valid without restriction

2.2 BOILING POINT

Value:	605° C
Pressure:	760 mm Hg
Decomposition:	No data
Method:	Adapted Stein and Brown method
GLP:	No
Remarks:	Estimation method based on molecular structure and measured melting point value.
Reference:	EPIWIN/MPBPWIN v1.40
Reliability:	(2) Valid with restrictions – Modelling data

2.3 DENSITY (relative density)

Type:	Density
Value:	1.69
Temperature:	25° C
Method:	Determination of density of solids by pycnometry
GLP:	No
Remarks:	None
Reference:	R. T. Vanderbilt Standard Method of Analysis (T-288)

Reliability:	(2) Valid with restrictions – methods other than pycnometry may be more reliable for determination of density of solids

2.4 VAPOUR PRESSURE

Value:	4.64 x 10^{-14} mm Hg
Temperature:	25 °C
Method:	calculated, modified Grain method
GLP:	No
Remarks:	Estimation method based on molecular structure and measured melting point value.
Reference:	EPIWIN/MPBPWIN v1.40
Reliability:	(2) Valid with restrictions – Modelling data

2.5 PARTITION COEFFICIENT $log_{10}P_{ow}$

Log Pow:	3.06
Temperature:	None
Method:	Other: SRC LogKow (KowWin) Program
GLP:	No
Remarks:	Estimation method based on molecular structure fragments
Reference:	EPIWIN/WSKO v1.40
Reliability:	(2) Valid with restrictions – Modelling data

2.6 WATER SOLUBILITY

A. Solubility

Value:	32 mg/l
Temperature:	20 °C
Description:	
Method:	OECD 105, OPPTS 830.7840
GLP:	Yes
Test substance:	As prescribed by 1.1-1.2, purity approximately 95%
Reference:	R. T. Vanderbilt study 860/072
Reliability:	(1) Valid without restrictions

B. pH Value, pKa Value

pH Value:	Not Applicable
pKa value	Not Applicable

2.11 OXIDISING PROPERTIES

No data available.

2.12 OXIDATION: REDUCTION POTENTIAL

No data available.

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd)

B. Other data – Henry's Law Constant

Results: 7.48×10^{-16} atm-m^3/mole
Remarks: Calculated at 25° C
Reference: EPIWIN/HENRYWIN v3.10
Reliability: (2) Valid with restrictions – Modelling data

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1.1 PHOTODEGRADATION

Type: Air
Light source: Sunlight
Temperature: 25°C
Direct photolysis:
Half life: 1.205 hours
Rate constant (radical): 106.4831×10^{12} cm^3/molecule-sec
Method: calculated
Atmospheric Oxidation Program/SAR Methods, 1995
GLP: No
Test substance: As prescribed by 1.1-1.2, purity approximately 95%
Remarks: Rapid atmospheric degradation of test substance in vapor phase by reaction with photochemically produced hydroxyl radicals. Particulate test substance may be physically removed from air by both wet and dry deposition. If released to air, test substance is expected to exist primarily in particulate phase.
Reference: EPIWIN/AOPWIN v1.90

3.1.2 STABILITY IN WATER

No data available. HYDROWIN v. 1.67 could not calculate rate constants for this structure.

3.2 MONITORING DATA (ENVIRONMENTAL)

No data available

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 TRANSPORT

Type: Adsorption
Media: Soil/Sediment
Method: Estimation method
Results: Koc = 3.22×10^3 ; Log Koc = 3.5081
Remarks: None
Reference: EPIWIN/PCKOCWIN v1.66

Reliability: (2) Valid with restrictions – Modelling data

Type: Volatilization
Media: Water
Method: Estimation Method
Results: Volatilization half-life from model river: 1.55 $x10^{12}$ hours
Volatilization half-life from model lake: 1.691 $x10^{13}$ hours
Remarks: Model river = 1 m deep flowing at 1 m/sec and wind velocity of 5 m/sec. Model lake = 1 m deep flowing at 0.05 m/sec and wind velocity of 0.5 m/se.
Reference: EPIWIN/HYDROWIN v1.67
Reliability: (2) Valid with restrictions – Modelling data

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Media: Air-water-soil-sediment
Method: Fugacity level III
EPIWIN v3.10
Results:

Mass Amount (%)		Half-life (hrs)	Emissions (kg/hr)
Air	0.0172	2.41	1000
Water	18.5	1440	1000
Soil	81	1440	1000
Sediment	0.436	5760	0

Remarks: Persistence time estimated to be 1400 hours
Reference: EPISUITE/EPIWIN v3.10
Reliability: (2) Valid with restrictions – Modelling data

3.5 BIODEGRADATION

Type: aerobic
Inoculum: non-adapted sludge
Concentration of the chemical: equivalent to 5 mg/l carbon
Medium: defined culture medium
Degradation: 27% CO_2 production after 28 days
Results: not readily biodegradable but ultimately biodegradable
Method: OECD 301B, EPA 835.3110
GLP: Yes
Test substance: As prescribed by 1.1-1.2, purity approximately 95%
Remarks: Test material was toxic to non-adapted organisms at recommended concentration of 10 mg/l carbon.
Reference: R. T. Vanderbilt study 860-081
Reliability: (1) valid without restrictions.

3.6 BOD5, COD OR RATIO BOD5/COD

No data available.

3.7 BIOACCUMULATION

Species: None (estimation)
BCF: 45.7
Type of test: Calculated
GLP: No data
Test substance: As prescribed by 1.1-1.2, purity approximately 95%
Remarks: None
Reference: BCFWIN v2.14

Reliability: (2) valid with restrictions – modelling data

4. ECOTOXICITY

4.1 ACUTE/PROLONGED TOXICITY TO FISH

No data available.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

No data available.

4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

No data available.

5. TOXICITY

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

Type:	LD_{50}
Species/strain:	Rat, Sherman-Wistar
Value:	800 mg/kg b.w.
Sex:	Male
# of Animals:	Five per group
Vehicle:	Corn Oil
Doses:	0, 0.5, 1.0, 2.0, 4.0, 8.0 ml/kg b.w.
Method:	Other
GLP:	No
Test substance:	As prescribed by 1.1-1.2, purity approximately 95%
Remarks:	Test material was administered as a 25% w/v suspension in corn oil. Graded doses were administered to five groups of five male adult rats. At 4.0 ml/kg (1.0 g/kg) animals were severely depressed within 12 hours of dosing; at 8.0 ml/kg, all animals died within the first day. No abnormalities were observed in any test animal on necropsy.
Reference:	R. T. Vanderbilt study 06/07/1977
Reliability:	(1) Valid without restriction.

5.1.2 ACUTE INHALATION TOXICITY

Type:	LC_{50} (4 hr)
Species/strain:	Rat, Sprague-Dawley
Value:	> 2.03 mg/l
Sex:	Male and female
# of Animals:	Five per group
Doses:	0, 2.13 mg/l
Method:	OECD 073, OPPTS 870.1300
GLP:	Yes
Test substance:	As prescribed by 1.1-1.2, purity approximately 95%

Remarks:	Test material was administered by nose-only exposure. Mass median aerodynamic diameter was 3.08 µ. There were no fatalities.
Reference:	R. T. Vanderbilt study 860-073
Reliability:	(1) Valid without restriction.

5.1.3 ACUTE DERMAL TOXICITY

Type:	LD_{50}
Species/strain:	Rat, Sprague-Dawley
Sex:	Male/female
# of Animals:	Five per sex
Vehicle:	None; arachis oil used to moisten the test material
Doses:	2,000 mg/kg b.w.
Exposure Time:	24 Hours
Value:	>2,000 mg/kg bow.
Method:	OECD 402, limit dose
GLP:	Yes
Test substance:	As prescribed by 1.1-1.2, purity approximately 95%.
Remarks:	Test material was moistened with arachis oil and applied to an area of shorn skin. All test animals received a single dermal exposure of 2,000 mg/kg b.w. The test material was held in place by surgical gauze and self-adhesive bandage. The semi-occlusive wrap was removed after 24 hours and the excess material was wiped from the test animal. There were no deaths, no signs of systemic toxicity, no signs of dermal irritation and all animals showed expected weight gain. No abnormalities were noted at necropsy
Reference:	R. T. Vanderbilt study 860-074
Reliability:	(1) Valid without restriction

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

Species/Strain:	Rabbits, New Zealand Albino
Results:	Slightly irritating
Classification:	Not irritating
Method:	Draize, J.H., Woodard, G., and Calvery, H.O., 1944
GLP:	Yes
Test substance:	As prescribed by 1.1-1.2, purity approximately 95%
Remarks:	The skin on the dorsal surface of six animals was shaved with an electric clipper. The skin on one side of the animal was abraded with a lancet, sufficiently deep to penetrate the stratum corneum but not deep enough to cause bleeding. One-half (0.5) gram of test material was applied to each of two intact and two abraded sites on each animal. Test material was applied to the skin under gauze patches and held in contact with the skin by an occlusive wrap. The occlusive wrap and gauze patches were removed after 24 hours. Treated areas were examined when test material was removed and 48 hours thereafter. Irritation was scored by the Draize Method; all scores were zero.
Reference:	R. T. Vanderbilt study 06/07/1977

Reliability:	(2) Valid with restrictions – Differs from current testing guidelines by using abraded skin surface, a 24-hr contact period rather than a 4-hr contact period.

5.2.2 EYE IRRITATION/CORROSION

Species/strain:	Rabbits, New Zealand Albino
Results:	Slightly irritating
Classification:	Not irritating
Method:	Draize, J.H., Woodard, G., and Calvery, H.O., 1944
GLP:	Yes
Test substance:	As prescribed in 1.1-1.2, purity approximately 95%
Remarks:	One-tenth (0.1) gram test material was instilled into the conjunctival sac of the right eye of each animal; the left eye remained untreated as control. Test material was not washed from the eyes. Observations for signs of irritation were conducted one hour after application and 1, 2, 3, 5 and 7 days after dosing. The Draize Method was used for scoring eye irritation. The average Draize score for 24, 48 and 72 hours was calculated for each animal and then averaged over the six animals. The average Draize score was 0.3 on a scale from 0-110. All signs of irritation had subsided by the second day after exposure.
Reference:	R. T. Vanderbilt study 06/07/1977
Reliability:	(1) Valid without restriction

5.4 REPEATED DOSE TOXICITY

No data available.

5.5 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

Type:	Ames Bacterial Reverse Mutation Assay
System of testing:	Salmonella typhimurium TA1535, TA1537, TA102, TA98, TA100
Concentration:	0, 50, 150, 500, 1500 and 5000 µg/plate
Metabolic activation:	With and Without
Results:	
Cytotoxic conc.:	With metabolic activation: 5,000 µg/plate Without metabolic activation: 5,000 µg/plate
Precipitate conc.:	>5,000 µg/plate
Genotoxic effects:	With metabolic activation: negative Without metabolic activation: negative
Method:	Ames *et al*., Mutation Res. 31: 347-364 (1975); OECD 471
GLP:	Yes
Test substance:	As prescribed in 1.1-1.2, purity approximately 95%
Remarks:	The test compound was evaluated for genetic activity in microbial assays with and without the addition of mammalian metabolic activation preparations. The *Salmonella typhimurium* strains used for this experiment were obtained from the University of California at Berkeley. The activation system used was S-9 homogenate from adult male Sprague-Dawley rat livers induced with phenobarbitone and ß-naphthoflavone. Positive controls for the non-activation assays were N-ethyl-N'-nitro-N-nitrosoguanidine, 9-aminoacridine, mitomycin C and 4-

nitroquinoline-1-oxide. Positive control chemicals used for the activation assays were 2-aminoanthracine, benzo(a)pyrene, and 1.8-dihydroxyanthaquinone.
Non-activation results: No mutagenic activity in any indicator organism at any dose.
Activation results: No mutagenic activity in any indicator organism at any dose.
A slight decrease in the frequency of revertant colonies was observed at the high dose.

Reference: R. T. Vanderbilt study 860-077
Reliability: (1) Valid without restriction

B. NON-BACTERIAL IN VITRO TEST

No data available.

5.6 GENETIC TOXICITY IN VIVO

No data available.

5.7 CARCINOGENICITY

No data available.

5.8 TOXICITY TO REPRODUCTION

No data available.

5.9 DEVELOPMENTAL TOXICITY/ TERATOGENICITY

No data available.

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities

No data available.

B. Toxicodynamics, toxicokinetics

No data available.

5.11 EXPERIENCE WITH HUMAN EXPOSURE

No data available.